

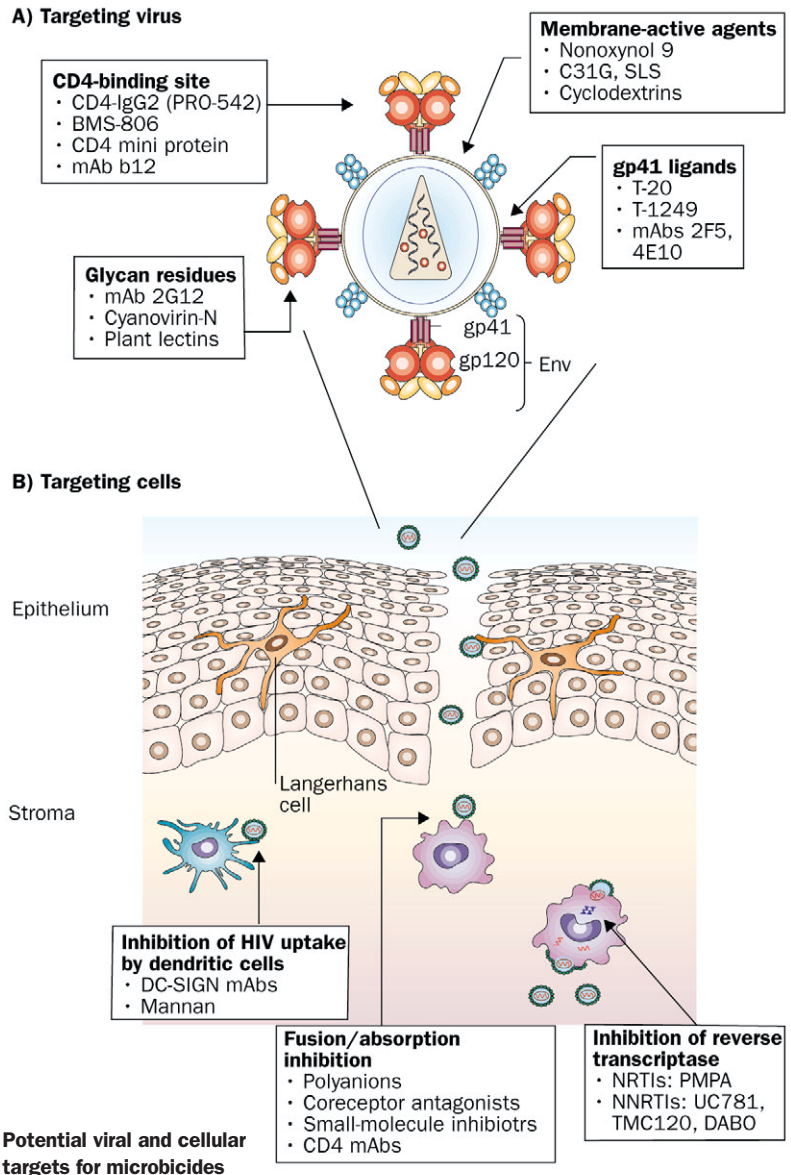
COMMENTARY

Microbicides—aims to safer sex

The continued growth of the global AIDS epidemic is testament to the lack of safe-sex practices.¹ In many developing countries, AIDS is taking a disproportionate toll on women and is one of the most serious women's health issues globally. In sub-Saharan Africa, women account for 58% of all adult HIV/AIDS cases, with half of these aged 15–24. Biologically, women may be up to four times more vulnerable to HIV infection.² Lack of economic and social power means that many women cannot negotiate safe sex, while the risk of being stigmatised as barren is often feared far more than the risk of HIV infection.³ On average, a woman who gets infected with HIV has only one partner—her husband.⁴ Thus there is an urgent need to develop discreet female-controlled prevention methods that aid safe sex.

Without an effective vaccine, increasing attention is being paid to the development of topical microbicides to prevent the sexual spread of HIV. Microbicides are topical formulations designed to block HIV-1 infection when applied vaginally (and possibly rectally) before intercourse.^{5,6} To be successful, such agents will have to be cheap, stable, easy to use, and acceptable to target populations. The earliest efforts to formulate vaginal microbicides against HIV were based on the non-specific disruption of viral particles by the surfactant nonoxynol 9, contained within many spermicides. However, nonoxynol 9 also destroyed membranes of epithelial cells lining the vagina and cervix, which serve as an important barrier to HIV infection. Thus in clinical trials nonoxynol 9 did not protect against HIV infection and increased the probability of acquiring infection in women who used the product many times a day.⁷ An important lesson learned from these early trials was that any potential microbicide must not reduce natural defences against HIV infection.

More recently, rapid advances in our understanding of the cell and molecular biology of HIV transmission and infection^{8,9} have led to the development of microbicides that specifically target mechanisms of HIV transmission without harming the body's natural defences.⁶ One approach is to target the incoming virus within infectious semen (figure, A). While some membrane-disruptive agents are still under consideration, the most appealing candidates interact with the viral envelope glycoproteins (gp120/41). These inhibitors include antibodies, proteins, and small-



Strategies aimed at targeting infectious virus within vaginal lumen include use of membrane-active agents (although use might be impractical due to potential toxicity). However, most viral-targeted agents under development are directed towards gp120 or gp41 components of HIV-1 Env protein complex. These agents include those able to block CD4-binding site, those targeting conserved glycan residues, and inhibitors of gp41-mediated fusion. Potential microbicide strategies that target susceptible cells within genital mucosa include blockade of HIV fusion and/or absorption, inhibition of reverse transcriptase, and prevention of HIV uptake by dendritic cells. Successful microbicide formulations may require combination products that target more than one step. mAbs=monoclonal antibodies, NRTI=nucleoside-analogue reverse-transcriptase inhibitor, NNRTI=non-nucleoside-analogue reverse-transcriptase inhibitor, DC-SIGN=DC-specific ICAM-grabbing integrin, PMPA=tenofovir. Adapted from ref 10 with permission.

molecule inhibitors able to bind to glycan residues or interfere with the CD4-binding/ coreceptor-binding-site of gp120, leading to irreversible viral inactivation.

An alternative is to target early stages in the viral life cycle

(figure, B). Such approaches include the use of polyanionic compounds that bind to the positively charged areas of gp120 (exposed on interaction with CD4), preventing subsequent coreceptor interaction. More specific targeting includes direct blockade of viral coreceptors (CCR5 or CXCR-4), preventing subsequent activation of the fusogenic gp41 protein, or direct targeting of gp41 itself with peptide and small-molecule inhibitors. A third way is to target the reverse-transcriptase enzyme, preventing proviral DNA formation before viral integration into the host-cell genome. Finally, because vaginal and cervical mucosae contain numerous dendritic cells capable of binding HIV in the absence of infection, any effective microbicide will have to block dendritic-cell-mediated uptake and transport of virus to draining lymph nodes.¹¹ Ultimately the most successful strategy may depend on combination products that target more than one step in the infection process.

There are still important challenges to overcome before an effective microbicide can be found. These challenges include manufacture at acceptable cost, appropriate and acceptable formulation, building of sufficient clinical-trial capacity to test multiple products, funding, and securing appropriate regulatory approval.

Finding a suitable microbicide will only be achieved by clinical trials. The Microbicides 2004 conference¹² on March 28–31 in London will see presentations of several macaque studies in which a range of potential candidates have shown protection against vaginal challenge with infectious virus—something that has not been achieved for the current vaccine candidates entering efficacy trials. If successful in clinical trials, first-generation products could be available by 2010, with second and third generations following close behind. But there is a substantial shortfall in the funding required to meet these targets. Current modelling suggests that microbicide use has the potential to yield major public-health gains. Any effect will depend on coverage, so even a low-efficacy microbicide used by a large number of women could be important. At 20% coverage, a microbicide of 60% effectiveness against HIV could avert up to 2.5 million HIV infections over 3 years.¹³ This effect translates into substantial health savings to already overstretched economies (US\$2.7 billion health savings and \$1.04 billion productivity gains over 3 years). Such savings could be critical to sustaining in-country provision of antiretroviral drugs for those already infected with HIV. Thus effective microbicides may not only be aids to safe sex, but they may also benefit AIDS treatment itself.

RS chairs the Basic Science Track Committee for Microbicides 2004 and will be giving a plenary talk at the meeting; SS is a committee member of the Microbicides 2004 Behavioral Science Track Committee. RS receives microbicide research grant funding from NIH (USA), MRC/DFID (UK), International Partnership on Microbicides, and EU (European Microbicide Programme).

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- UNAIDS. AIDS epidemic update. 2003: <http://www.unaids.org/Unaid/EN/Resources/Publications/corporate+publications/aids+epidemic+update+-+december+2003.asp> (accessed March 18, 2004).
- Baeten JM, Overbaugh J. Measuring the infectiousness of persons with HIV-1: opportunities for preventing sexual HIV-1 transmission. *Curr HIV Res* 2003; **1**: 69–86.
- Newman S, Sarin P, Kumarasamy N, et al. Marriage, monogamy and HIV: a profile of HIV infected women in South India. *Int J STD AIDS* 2000; **11**: 250–53.
- Solomon S, Buck J, Chaguturu S, Ganesh AK, Kumarasamy N. Stopping HIV before it begins; issues faced by women in India. *Nat Immunol* 2003; **4**: 719–21.

- Stone A. Microbicides: a new approach to preventing HIV and other sexually transmitted infections. *Nat Rev Drug Discov* 2002; **1**: 977–85.
- Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. *Nat Rev Microbiol* 2003; **1**: 25–34.
- Van Damme L, Ramjee G, Alary M, on behalf of the COL-1492 Study Group. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360**: 971–77.
- Miller CJ, Shattock RJ. Target cells in vaginal HIV transmission. *Microbes Infect* 2003; **5**: 59–67.
- Pope M, Haase AT. Transmission, acute HIV-1 infection and the quest for strategies to prevent infection. *Nat Med* 2003; **9**: 847–52.
- Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. *Nat Rev Microbiol* 2003; **1**: 25–34.
- Hu Q, Frank I, Williams V, et al. Blockade of attachment and fusion receptors inhibits HIV-1 infection of human cervical tissue. *J Exp Med* (in press).
- Microbicides 2004. 28–31 March 2004–Hilton London Metropole. <http://www.microbicides2004.org.uk> (accessed March 16, 2004).
- Watts C, Vickerman P. The impact of microbicides on HIV and STD transmission: model projections. *AIDS* 2001; **15** (suppl 1): S43–44.

Head size and autism

50 years after Kanner's original 1943 description¹ of large heads in autism, Bailey et al² reintroduced the possibility of a relation between abnormalities in head size or brain volume and autism. In 1997, Stevenson et al³ found that macrocephaly was the single most consistent physical characteristic of children with autism. A subsequent study⁴ concluded that macrocephaly is an independent trait in autism. Compared with that in healthy volunteers, brain development in autism is abnormal, with accelerated growth in early life that results in brain enlargement in childhood.⁵ Brain volume in adolescents and adults with autism is, however, normal,^{6,7} probably because of a slight decrease in brain volume at the same time as normal children are having a slight increase.

Recently, Monica Conciatori and colleagues⁸ showed an association between the *HOXA1* gene, which has a critical role in the development of hindbrain neural structures, and autism. In a combined case-control and family-based association design, these researchers showed that the *HOXA1* A218G polymorphism contributed significantly to findings of large head-circumference in patients with autism. Although it is unclear whether this genotype-phenotype correlation is specific to autism, or related to large head-circumference more generally, this study corroborates the usefulness of head circumference as a potential endophenotype in autism.

Courchesne et al⁹ examined historical data, clinical indices, and MRI in 48 children aged 2–5 years who were diagnosed as having autistic spectrum disorder (ASD), in comparison with typically developing children. The main findings were, first, that head circumference at birth in the ASD group was smaller than average for all infants at birth; body length and weight averages were the same. Second, for children with autism compared with all children of similar ages, head size increased rapidly beginning several months after birth and correlating with increases in cerebral and cerebellar volumes by ages 2–5 years. This excessive brain growth slowed by middle to late childhood, so that by adolescence and adulthood head and brain size of individuals with ASD did not differ significantly from the healthy average. Third, the earlier the onset, the faster the rate, and the longer the period of excessive brain growth, the more severe the ASD.

In an earlier study from the same group,¹⁰ regional variation of brain volume was examined in boys aged 2–11 years with autism and in age-matched typically developing boys. At ages 2–3 years, boys with autism had significant